REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 8-19 and 23-31 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

It is noted on the Office Action Summary that none of the certified copies of the priority documents have been received. Applicants however point out this application is a continuation-in-part of a 371 national stage application (parent application no. 09/423,398), in which a priority document is indicated as being received on the Notification of Acceptance of Application Under 35 USC 371 and 37 CFR 1.494 or 1.495 dated March 3, 2000. Accordingly, applicants request that the examiner indicate in the next Office Action that a certified copy of the Israeli priority document was received in parent application no. 09/423,398.

Non-elected claims 1-7 and 20-22 are now cancelled without prejudice to filing a divisional application thereon. The requirement for restriction is again respectfully traversed insofar as claims 10, 11 and 13, and SEQ ID NOs: 5-8 are concerned.

The examiner stated that applicants' argument that the remaining sequences are structurally and functionally similar is not persuasive because SEQ ID NOs: 1 and 2 do not contain the inserted amino acid sequences which make these sequences unique, and therefore, require separate searches for these unique sequences. However, as

disclosed at page 20, paragraph 0071, human muscle AchR α-subunit exists as two isoforms of 437 and 462 amino acid residues, which are identical except for a 25 additional residue insertion (encoded by the 75bp exon p3A) after residue 58 in the extracellular domain of the longer isoform. Claim 8 is now amended to be generic for the amino acid sequences of SEQ ID NO:2, 4, 6, and 8 (SEQ ID NOs:1, 3, 4, and 7 are nucleotide sequences that encode SEQ ID NOs: 2, 4, 6, and 8) by reciting the critical residues that are common to these sequences and which would only require a single search. At least the restriction requirement with respect to the sequences should be restated as an election of species requirement in which SEQ ID NOs:1 and 2 are the elected species, if the requirement is not withdrawn altogether.

It is further noted that the examiner referred to a complete reply to a final rejection at the bottom of page 2 of the Office Action. Applicants respectfully point out that there is no final rejection as the present Office Action is a first Office Action on the merits.

Claims 8-9 and 17 have been rejected under 35 U.S.C. §101. The examiner's suggestion is adopted, thereby obviating this rejection.

Claims 8-9, 12, and 14-19 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Claim 8 is amended to recite that the polypeptide encoded by the DNA molecule comprises residues 61-76 of SEQ ID NO:2 and/or residues 184-210 of SEQ ID NO:2, which are disclosed in the paragraph bridging pages 24 and 25 of the specification as being the main immunogenic region and the acetylcholine binding site, respectively. Furthermore, the recitation of at least 70% sequence homology in claim 9 is now deleted without prejudice. The amendments to the claims obviates this rejection.

Claim 8 also recites for a polypeptide embodiment with at least 95% sequence identity as supported by the specification at the bottom of page 22. Example 14 (Product by Function) of the Revised Interim Written Description Guidelines Training Materials is also directed to variants of a specific sequence for which an activity is essential to the operation of the claimed invention. As discussed below with regard to the enablement rejection, assays for identifying other polypeptides that have the claimed function is disclosed in the specification.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 8-9, 12, and 14-19 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, while being enabling for the specific DNA of SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:2, does not reasonably provide enablement for any encoded biological functional equivalent polypeptides/fragments with little structural characterization and no

distinguishable recited functional characteristics. This rejection is believe to be obviated by the amendment to the claims.

The present specification at pages 26-28 discloses that:

> The best effect as a toleragen appears to occur when the polypeptide according to the present invention is allowed to assume a conformation which is farthest from its native conformation.

It is further disclosed at the same pages and that there are several ways to routinely test for how close the polypeptide is to the native conformation of AchR α-subunit. One of skill in the art can test by strength of binding of the polypeptide to α-bungarotoxin (αBTX) or to monoclonal antibody 198. As disclosed at the bottom of page 27, these tests can be performed on fragments, analogs and chemical derivatives to determine suitability as a toleragen for administration to a patient suffering from myasthenia gravis. Moreover, as positively recited by amended claim 8, the polypeptide encoded by the DNA of the present invention must include one or both of (1) residues 61-76 of SEQ ID NO:2 (main immunogenic region) and (2) residues 184-210 (acetylcholine binding site) without any changes within these sequences. Thus, these residues are critical and it is in the flanking residues where changes can be made within the parameter of "at least 95% sequence identity" that causes changes that make the conformation of the polypeptide less like the native conformation of AchR α-subunit. One of skill in the art is far more enabled to make amino acid changes that affect the conformation of the polypeptide given the guidance provided by the specification than to make changes that would not affect the

conformation. Accordingly, one of skill in the art is fully enabled for the scope of the claims as presently appear in this application.

With regard to the examiner's reference to the polypeptide encoded by the DNA of the present invention as an antibody blocking peptide and the examiner's comment that random mutations or modifications would be predicted to adversely alter its biologically active 3-dimensional conformation and therefore the antigenic site itself, applicants emphasize the polypeptide encoded by the DNA of the present invention do not act simply by blocking the undesirable autoantibodies, but rather act on the immune system in a more complicated manner. Therefore, mutations or alterations could improve the ability of polypeptides to induce tolerance even though their capacity to bind to (and block) the autoantibodies would be reduced.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 8-9, 12 and 14-19 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendments to the claims.

Claims 8-9, 12, 14 and 16-19 have been rejected under 35 U.S.C. §102(b) as being anticipated by Schoepfer et al. (1988). The examiner states that Schoepfer teaches isolation of a human AchR DNA that encodes a polypeptide inherently capable of modulating the autoimmune response of an individual to the acetylcholine receptor, which comprises nucleotides 1 to 363 and nucleotides 364 to 630 of SEQ ID NO:1 as well as the fusion of any or all fragments of SEQ ID NO:1. This rejection is respectfully traversed.

As amended, claim 8 recites for a polypeptide using the closed language "consisting of" and therefore cannot anticipated by the full length AchR α-subunit nucleotide and encoded amino acid sequences disclosed by Schoepfer. Furthermore, claim 8 no longer recites for two or more fragments of (vii) fused together with or without a spacer, thereby mooting this issue.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 8-9, 12, 14, and 16-19 have been rejected under 35 U.S.C. §102(b) as being anticipated by Talib et al. (1991; IDS Ref. AM). The examiner states that Talib teaches isolation of a human AchR DNA that encodes a polypeptide inherently capable of modulating the autoimmune response of an individual to the acetylcholine receptor, which comprises nucleotides 1 to 363 and nucleotides 364 to 630 of SEQ ID NO:1, as well as the fusion of any or all fragments of SEQ ID NO:1. This rejection is respectfully traversed.

As amended and discussed above, claim 8 recites for a polypeptide using the closed language "consisting of" and therefore cannot be anticipated by the full length AchR α-subunit nucleotide and encoded amino acid sequences disclosed by Talib. Furthermore, claim 8 no longer recites for two or more fragments of (vii) fused together with or without a spacer, thereby mooting this issue.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

The examiner holds that the Information Disclosure Statement filed 3/29/01 fails to comply with 37 CFR 1.98(a)(2), which requires a

legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The examiner indicates that the references listed on the PTO-1449 form have not been considered.

In response, the examiner's attention is directed to 37 CFR 1.98(d), which states that a copy of the reference is required to be provided unless (1) the earlier application in which a copy of the reference was previously submitted is properly identified and relied on for an earlier filing date under 35 U.S.C. 120 and (2) the IDS submitted in the earlier application complies with 1.98(a) through (c). An IDS in full compliance with 37 CFR §1.98(a) through (c) was submitted in parent application no. 09/423,398 on March 8, 2000. Parent application no. 09/423,398 is properly identified and relied on for an earlier filing date under 35 U.S.C. 120 in the "Cross-Reference to Related Applications" section on page 1 of the instant application as well as on the transmittal letter for filing of the instant continuation-in-part application. On page 2 of the transmittal letter filed with the application on March 29, 2001, it is indicated that applicants identify documents previously cited or submitted to the USPTO by attaching a PTO-1449 form listing these documents, and that no copies of these documents need be filed in the present application pursuant to 37 CFR 1.98(d). As a convenience to the examiner, a clean PTO-1449 form listing the references previously submitted along with courtesy copies of the listed references are attached hereto for the examiner's consideration. The examiner is requested to consider the

references listed on PTO-1449 and provide an initialed PTO-1449 form with the next communication from the USPTO.

Each of new claims 23-30 is directed to a separate subsection (i)-(viii) of claim 8. The feature of an additional polypeptide being glutathione S-transferase is supported in the specification at page 25, paragraph 0082.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\Y\YEDA\fuchs2A\pto\Amendment B.doc